cavity to release the drug.

Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration and dosage employed for each subject is left to the discretion of the practitioner.

In general, the dosage of invention conjugate employed as described herein falls in the range of about 0.01 mmoles/kg body weight of the subject/hour up to about 0.5 mmoles/kg/hr. Typical daily doses, in general, lie within the range of from about 10 μg up to about 100 mg per kg body weight, and, preferably within the range of from 50 μg to 10 mg per kg body weight and can be administered up to four times daily. The daily IV dose lies within the range of from about 1 μg to about 100 mg per kg body weight, and, preferably, within the range of from 10 μg to 10 mg per kg body weight.

In accordance with yet another embodiment of the present invention, there are provided improved methods for the treatment of a subject suffering from a pathological condition by administration thereto of a NSAID and/or a selective COX-2 inhibitor, the improvement comprising covalently attaching said NSAID to said selective COX-2 inhibitor prior to administration thereof to said subject.

Thus, invention method for the treatment of a subject afflicted with a pathological condition comprises administering to a subject an effective amount of a modified pharmacologically active agent,

wherein said pharmacologically active agent is a NSAID or a selective COX-2 inhibitor, and is effective for treatment of said condition, and

wherein said pharmacologically active agent has been modified by the covalent attachment thereto of a NSAID or a selective COX-2 inhibitor.

The invention will now be described in greater detail by reference to the following non-limiting examples.

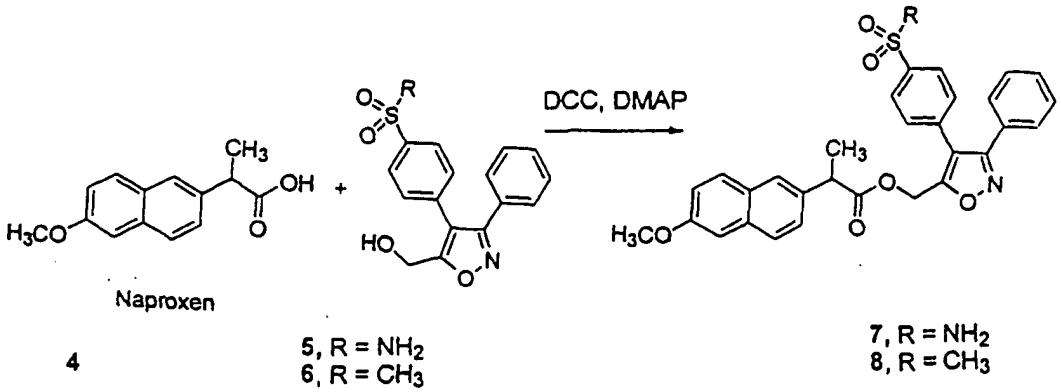
## Example 1

**General procedure for the preparation of conjugate compound 3 (Scheme 1).** To a stirring solution of NSAID compound (**1**) (1 eq), COX-2 inhibitor (**2**) (1 eq) and dimethylaminopyridine (DMAP) (0.2 eq) in anhydrous THF is added 1,3-dicyclohexylcarbodiimide (DCC) (1 eq) at 0 °C. The resulting solution is stirred at room temperature for several hours. The reaction solution is filtered and the solvent is evaporated. The residue is partially dissolved in ethyl acetate, the solid is filtered off and the solution is washed with 0.5 N HCl, saturated sodium bicarbonate solution and brine. After the solvent is evaporated, the compound is purified either by flash chromatography or crystallization to give compound **3**.

## Example 2

The synthesis described in this and the following example is illustrated in Scheme 2:

## SCHEME 2



Compound 7 **(Scheme 2)**. Compound 7 is prepared as described in the general procedure above for compound 3 from naproxen (2.30g, 10 mmol), compound 5 (3.30g, 10 mmol), DMAP (0.24g, 2 mmol) and DCC (2.06g, 10 mmol). The compound is purified by column chromatography on a silica gel column to give compound 7 with a yield from 50% to 80%.

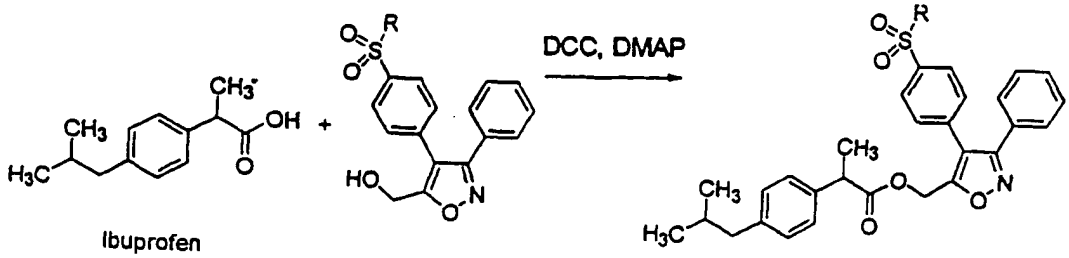
## Example 3

Compound 8 **(Scheme 2)**. Compound 8 is prepared as described in the general procedure above for compound 3 from naproxen (2.30g, 10 mmol), compound 6 (3.29g, 10 mmol), DMAP (0.24g, 2 mmol) and DCC (2.06g, 10 mmol). The compound is purified by column chromatography on a silica gel column to give compound 8 with a yield from 50% to 80%.

## Example 4

The synthesis described in this and the following example is illustrated in Scheme 3:

## SCHEME 3




9 5, R = $NH_2$; 6, R = $CH_3$ 10, R = $NH_2$; 11, R = $CH_3$

Compound 10 **(Scheme 3)**. Compound 10 is prepared as described in the general procedure above for compound 3 from ibuprofen (2.06g, 10 mmol), compound 5 (3.30g, 10 mmol), DMAP (0.24g, 2 mmol) and DCC (2.06g, 10 mmol).

The compound is purified by column chromatography on a silica gel column to give compound **10** with a yield from 50% to 80%.

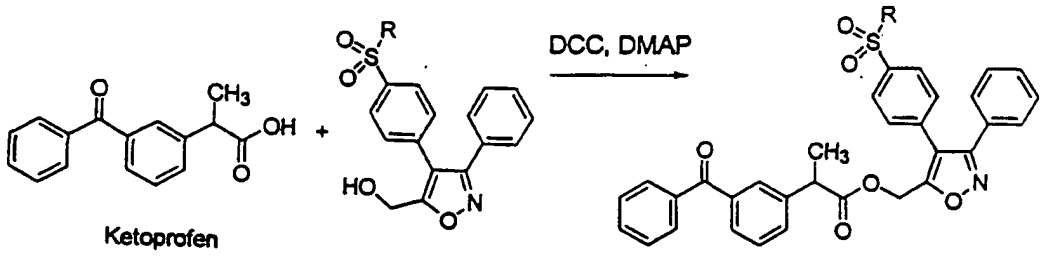
## Example 5

Compound **11** (**Scheme 3**). Compound **11** is prepared as described in the general procedure above for compound **3** from ibuprofen (2.06g, 10 mmol), compound **6** (3.29g, 10 mmol), DMAP (0.24g, 2 mmol) and DCC (2.06g, 10 mmol). The compound is purified by column chromatography on a silica gel column to give compound **11** with a yield from 50% to 80%.

## Example 6

The synthesis described in this and the following example is illustrated in Scheme 4:

## SCHEME 4




Compound **13** (**Scheme 4**). Compound **13** is prepared as described in the general procedure above for compound **3** from ketoprofen (2.54g, 10 mmol), compound **5** (3.30g, 10 mmol), DMAP (0.24g, 2 mmol) and DCC (2.06g, 10 mmol). The compound is purified by column chromatography on a silica gel column to give compound **13** with a yield from 50% to 80%.

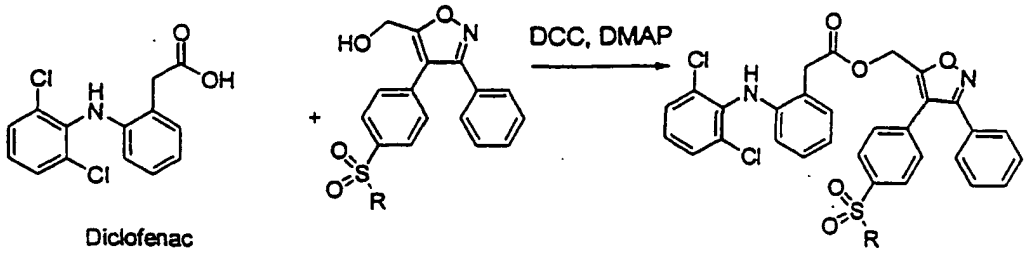
## Example 7

Compound **14** (**Scheme 4**). Compound **14** is prepared as described in the general procedure above for compound **3** from ketoprofen (2.54g, 10 mmol), compound **6** (3.29g, 10 mmol), DMAP (0.24g, 2 mmol) and DCC (2.06g, 10 mmol). The compound is purified by column chromatography on a silica gel column to give compound **14** with a yield from 50% to 80%.

## Example 8

The synthesis described in this and the following example is illustrated in Scheme 5:

## SCHEME 5




Compound **16** (**Scheme 5**). Compound **16** is prepared as described in the general procedure above for compound **3** from diclofenac (2.96g, 10 mmol), compound **5** (3.30g, 10 mmol), DMAP (0.24g, 2 mmol) and DCC (2.06g, 10 mmol). The compound is purified by column chromatography on a silica gel column to give compound **16** with a yield from 50% to 80%.

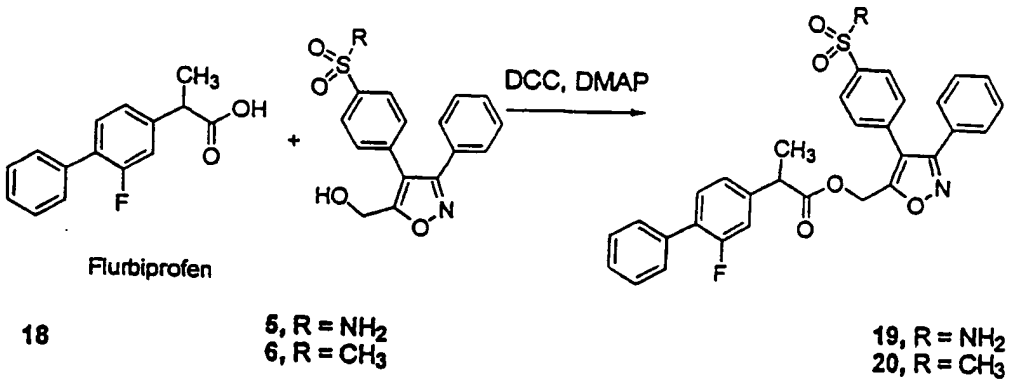
## Example 9

Compound **17** (**Scheme 5**). Compound **17** is prepared as described in the general procedure above for compound **3** from diclofenac (2.96g, 10 mmol), compound **6** (3.29g, 10 mmol), DMAP (0.24g, 2 mmol) and DCC (2.06g, 10 mmol). The compound is purified by column chromatography on a silica gel column to give compound **17** with a yield from 50% to 80%.

## Example 10

The synthesis described in this and the following example is illustrated in Scheme 6:

## SCHEME 6




**18**

**5**, R = $NH_2$
**6**, R = $CH_3$

**19**, R = $NH_2$
**20**, R = $CH_3$

Compound **19** (**Scheme 6**). Compound **19** is prepared as described in the general procedure above for compound **3** from flurbiprofen (2.44g, 10 mmol), compound **5** (3.3g, 10 mmol), DMAP (0.24g, 2 mmol) and DCC (2.06g, 10 mmol). The compound is purified by column chromatography on a silica gel column to give compound **19** with a yield from 50% to 80%.

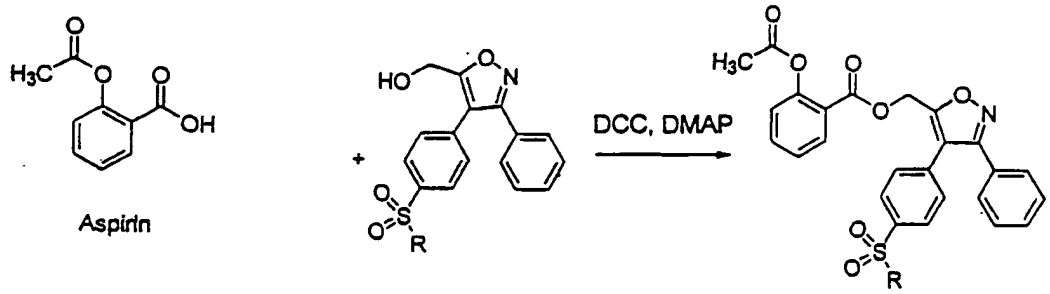
**Example 11**

Compound **20** (**Scheme 6**). Compound **20** is prepared as described in the general procedure above for compound **3** from flurbiprofen (2.44g, 10 mmol), compound **6** (3.29g, 10 mmol), DMAP (0.24g, 2 mmol) and DCC (2.06g, 10 mmol). The compound is purified by column chromatography on a silica gel column to give compound **20** with a yield from 50% to 80%.

**Example 12**

The synthesis described in this and the following example is illustrated in Scheme 7:

**SCHEME 7**




**21**

**5**, R = $NH_2$
**6**, R = $CH_3$

**22**, R = $NH_2$
**23**, R = $CH_3$

Compound **22** (**Scheme 7**). Compound **22** is prepared as described in the general procedure above for compound **3** from aspirin (1.80g, 10 mmol), compound **5** (3.30g, 10 mmol), DMAP (0.24g, 2 mmol) and DCC (2.06g, 10 mmol). The compound is purified by column chromatography on a silica gel column to give compound **22** with a yield from 50% to 80%.

## Example 13

Compound **23** (**Scheme 7**). Compound **23** is prepared as described in the general procedure above for compound **3** from aspirin (1.80g, 10 mmol), compound **6** (3.29g, 10 mmol), DMAP (0.24g, 2 mmol) and DCC (2.06g, 10 mmol). The compound is purified by column chromatography on a silica gel column to give compound **23** with a yield from 50% to 80%.

## Example 14

**Evaluation of the effects of the conjugate of naproxen and selective COX-2 inhibitor of the invention on acute gastric mucosal injury**

Wistar rats (200-250 grams, male) are fasted overnight but allowed free access to water. Ten rats in each group are given naproxen, selective COX-2 inhibitor or an invention conjugate thereof orally at doses of 10, 20 or 50 mg/kg. The rats are sacrificed five hours later and the visible gastric damage is assessed by examining under microscope and by histological evaluation.

For all three doses used, invention conjugate produces the least visible gastric lesions, compared to the lesions induced by either naproxen or COX-2 inhibitor alone. This is attributed to the stability and inactivity of the invention conjugate in the stomach, thereby reducing local irritation and damage.

## Example 15

**Evaluation on the anti-inflammatory effects of the conjugate of naproxen and selective COX-2 inhibitor of the invention**

Wistar rats (male, 200-250 grams) are fasted overnight but allowed to free access to drinking water. Naproxen, selective COX-2 inhibitor or an invention conjugate thereof is given orally at a dose of 1, 10 or 30 mg/kg (6 animals per group).

After one hour, the rats are anesthetized and 0.1 ml of lambda carrageenan (0.1% solution) is injected into the right hind foot pad. The volume of the pad is measured by hydroplethysmometry every hour for the next five hours.

The control group (given saline orally) shows a time-dependent increase in the volume of the footpad to near 0.7- 1.0 ml at the five-hour time point. On the other hand, all three treated groups reveal a dose-dependent reduction of the volume of the footpad. This suggests that the invention conjugate is as effective as either naproxen or COX-2 inhibitor administered alone for alleviation of acute inflammation induced by carrageenan, implying that upon in vivo absorption, naproxen and COX-2 inhibitor are released from the invention conjugate in the circulation and are fully active to exert their anti-inflammatory effects.

## Example 16

**Evaluation of the effects of the conjugate of naproxen and selective COX-2 inhibitor on prostaglandin synthesis**

Wistar rats (male, 200-250 grams) are fasted overnight but allowed free access to drinking water. The rats are anesthetized and their backs are shaved. After an incision to the back, a sponge (2.5 x 1 x 0.5 cm) soaked with 2 ml of 0.5% carrageenan is implanted. Five hours later, the rats (6 animals in each group) are given orally naproxen, selective COX-2 inhibitor or an invention conjugate thereof at a dose of 30 mg/kg or vehicle control. One hour later, the rats are sacrificed and the sponge is carefully removed. The exudate is recovered from the sponge and the prostaglandin E2 level in the exudate is measured by enzyme-linked immunosorbent assay.

In the control group (saline orally), the prostaglandin levels in the recovered exudates increase with time from 300 pg/ml to over 3000 pg/ml. In contrast, all three treated groups show substantial decreases in prostaglandin levels. The increase in prostaglandin levels is indicative of inflammatory reaction. The results suggest that

the invention conjugate is cleaved in vivo, thereby releasing both naproxen and COX-2 inhibitor and exerting anti-inflammatory activities.

## Example 17

**The effects of the conjugate of naproxen and selective COX-2 inhibitor on chronic hindlimb inflammation in the rat adjuvant arthritis model**

Lewis male rats (175 – 250 grams) are injected intradermally in the footpad with M. tuberculosis powder suspended in mineral oil at 5 mg/ml. Rats are dosed daily by oral gavage with 5 ml/kg of naproxen or selective COX-2 inhibitor at 1 and 10 mg/kg or equimolar doses of invention conjugate on days 5-8 and 11-14. Progressive swelling of the uninjected paw and ankle joint between days 11 and 15 are measured by plethysmometry.

In this rat adjuvant arthritis study, at day 15 the volume of the footpad in the control group (saline orally) increases by 1.5 to 2.0 ml over that of the untreated normal rats. However, all three treated groups show great reduction in the volume of the footpad at day 15, suggesting that all three agents, naproxen alone, COX-2 inhibitor alone and invention conjugate are equally effective as anti-arthritic treatment agents. This example demonstrates that the invention conjugate is readily converted into the active components of naproxen and COX-2 inhibitor in vivo in the circulation upon absorption in the intestines.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

That which is claimed is:

1. A compound having the structure:

X-L-Y

wherein:

X = a non-steroidal anti-inflammatory drug (NSAID),

L = an optional linker/spacer, and

Y = a selective COX-2 inhibitor.

2. A compound according to claim 1 wherein said NSAID is acetaminophen, aspirin, ibuprofen, choline magnesium salicylate, choline salicylate, diclofenac, diflunisal, etodolac, fenprofen calcium, flurobiprofen, indomethacin, ketoprofen, carprofen, indoprofen, ketorolac tromethamine, magnesium salicylate, meclofenamate sodium, mefenamic acid, oxaprozin, piroxicam, sodium salicylate, sulindac, tolmetin, meloxicam, nabumetone, naproxen, lornoxicam, nimesulide, indoprofen, remifenzone, salsalate, tiaprofenic acid, or flosulide.

3. A compound according to claim 2 wherein said NSAID is naproxen, aspirin, ibuprofen, flurbiprofen, indomethacin, ketoprofen, or carprofen.

4. A compound according to claim 1 wherein said selective COX-2 inhibitor is celecoxib, rofecoxib, valdecoxib, or derivatives.

5. A compound according to claim 4 wherein said selective COX-2 inhibitor is valdecoxib or derivatives thereof.

6. A compound according to claim 1 wherein L has the structure:

-Z-W-, -W-Z-, or –W-Z-W-,

wherein:

Z is alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, heterocyclic, substituted heterocyclic, oxyalkylene, substituted oxyalkylene, alkenylene, substituted alkenylene, arylene, substituted arylene, alkarylene, substituted alkarylene, aralkylene or substituted aralkylene, and

each W is independently ester, reverse ester, thioester, reverse thioester, amide, reverse amide, phosphate, phosphonate, sulfone, salfonamide, immine or enamine.

7. A formulation comprising a compound according to claim 1 in a pharmaceutically acceptable carrier therefor.

8. A formulation according to claim 7 wherein said pharmaceutically acceptable carrier is a solid, solution, emulsion, dispersion, micelle or liposome.

9. A formulation according to claim 7 wherein said pharmaceutically acceptable carrier further comprises an enteric coating.

10. In the administration of a non-steroidal anti-inflammatory drug (NSAID) and/or a selective COX-2 inhibitor to a subject for the treatment of a pathological condition, the improvement comprising covalently attaching said NSAID to said selective COX-2 inhibitor prior to administration thereof to said subject.

11. In the treatment of a subject suffering from a pathological condition by administration thereto of a non-steroidal anti-inflammatory drug (NSAID) and/or a selective COX-2 inhibitor, the improvement comprising covalently attaching said NSAID to said selective COX-2 inhibitor prior to administration thereof to said subject.

12. A method for the treatment of a subject afflicted with a pathological condition, said method comprising administering to said subject an effective amount of a non-steroidal anti-inflammatory drug (NSAID),

wherein said NSAID is effective for treatment of said condition, and

wherein said NSAID has been modified by the covalent attachment thereto of a selective COX-2 inhibitor.

13. A method for the preparation of a protected form of a non-steroidal anti-inflammatory drug (NSAID), said method comprising covalently attaching a selective COX-2 inhibitor to said NSAID.

14. A method for reducing the side effects induced by administration of a non-steroidal anti-inflammatory drug (NSAID) to a subject, said method comprising covalently attaching a selective COX-2 inhibitor to said NSAID prior to administration to said subject.

15. A method for enhancing the effectiveness of a non-steroidal anti-inflammatory drug (NSAID), said method comprising covalently attaching a selective COX-2 inhibitor to said NSAID.

16. A method for the treatment of a subject afflicted with a pathological condition, said method comprising administering to said subject an effective amount of a selective COX-2 inhibitor,

wherein said selective COX-2 inhibitor is effective for treatment of said condition, and

wherein said selective COX-2 inhibitor has been modified by the covalent attachment thereto of a non-steroidal anti-inflammatory drug (NSAID).

17. A method for the preparation of a protected form of a selective COX-2 inhibitor, said method comprising covalently attaching a non-steroidal anti-inflammatory drug (NSAID) to said selective COX-2 inhibitor.

18. A method for reducing the side effects induced by administration of a selective COX-2 inhibitor to a subject, said method comprising covalently attaching a non-steroidal anti-inflammatory drug (NSAID) to said selective COX-2 inhibitor prior to administration to said subject.

19. A method for enhancing the effectiveness of a selective COX-2 inhibitor, said method comprising covalently attaching a non-steroidal anti-inflammatory drug (NSAID) to said selective COX-2 inhibitor.

20. A method for the prevention or treatment of an inflammatory or infectious disease in a subject in need thereof, said method comprising administering to said subject an amount of the compound of claim 1 effective to alleviate said condition.

# INTERNATIONAL SEARCH REPORT

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**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A01N 37/36, 37/18, 31/16, 37/10, 37/44, 43/38; A61K 31/40
US CL : 514/159, 165, 629, 570, 567, 420

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MEDLINE, CAPLUS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 6,025,353 A (MASFERRER et al) 15 February 2000 (15.02.2000), see entire document. | 1-20 |
| A | US 5,607,966 A (HELLBERG et al) 04 March 1997 (04.03.1997), see entire document. | 1-20 |
| A | US 5,603,959 A (HORROBIN et al.) 18 February 1997 (18.02.1997), see entire document. | 1-20 |

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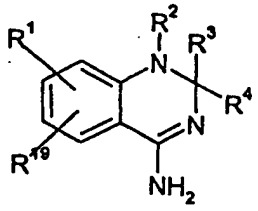
(54) Title: A PHARMACEUTICAL COMBINATION COMPRISING A COX-2 INHIBITOR AND A iNOS INHIBITOR



(I)

(57) Abstract

The invention relates to the co-administration of an inhibitor of induced nitric oxyde synthase of formula (I) and an inhibitor of cyclooxygenase-2 for the treatment of inflammation and inflammatory disorders.

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# A PHARMACEUTICAL COMBINATION COMPRISING A COX-2 INHIBITOR AND A iNOS INHIBITOR

The present invention relates to the co-administration of an inhibitor of induced nitric oxide synthase and an inhibitor of cyclooxygenase-2 for the treatment of inflammation and inflammatory disorders, such as arthritis, inflammatory bowel disease and CNS inflammatory disorders.

The excessive production of nitric oxide (NO) has been implicated in immune and inflammatory responses and as an important and novel mechanism in the pathology of a variety of chronic inflammatory diseases (Moncada S. et al, *Pharmacol. Rev.*, 1991, **43**, 109). The role of NO, as either a beneficial physiological mediator, or as pathological cytotoxic radical, is largely determined by the level and extent of synthesis. Under physiological conditions only low levels of NO are required for effector functions, whereas excessive NO production may be detrimental and pathological.

The synthesis of NO from the semi-essential amino acid L-arginine is catalysed by three different enzyme isoforms: endothelial NOS (eNOS) and neuronal NOS (nNOS) are constitutively expressed, calcium dependent enzymes and play a major role in normal physiology. The third major NOS isoform, inducible NOS (iNOS) is not expressed under physiological conditions but requires induction. Inflammatory stimuli, such as endotoxin and the cytokines interleukin-1 (IL-1), tumour necrosis factor-$\alpha$ (TNF$\alpha$) or interferon gamma (INF$\gamma$), induce *de novo* formation of a calcium independent NOS in a variety of cells, including epithelial cells, macrophages and neutrophils. The inducible NOS (iNOS) produces much greater amounts of NO for longer periods compared to the constitutive enzymes.

There is considerable evidence for an important role for iNOS in inflammation. The excessive NO production following induction of NO synthase plays an important role in the vascular permeability in intestinal inflammation produced by endotoxin . Inhibitors of iNOS attenuate the increase in plasma leakage (Boughton-Smith N. K. et al, *Eur. J. Pharmacol.*,

1990, **191**, 485). Inhibitors of iNOS reduce plasma leakage produced in zymosan peritonitis and by carrageenan in the rat paw and air pouch, in which there are increases in iNOS activity (Ialenti A., *Eur. J. Pharmacol.*, 1992, **211**, 177; Salvamini D. et al, *J. Clin. Invest.*, 1995, **96**, 301; Salvemini D. et al, *Br. J. Pharmacol.*, 1996, **118**, 829; Boughton-Smith N.K. and Ghelani A., *Inflamm. Res.*, 1995, Suppl. 2, S149). In rat adjuvant arthritis there are increases in plasma nitrite and NO production by peritoneal macrophages and immunoreactive iNOS is localised to synovial tissue. Paw swelling, loss in weight gain, synovial inflammation and cartilage degradation are reduced by the non-selective NOS inhibitors L-NAME and L-NMMA (Ialenti A. et al, *Br. J. Pharmacol.*, 1993, **110**, 701; Stefanovic-Racic M., *Arthritis and Rheumatism,* 1994, **37**, 1062; Stefanovic-Racic M. et al, *Rheumatol.*, 1995, **22**, 1922). Inhibitors of NOS also have beneficial effects in a rat model of arthritis induced by streptococcal cell wall (McCartney-Frances N., *J. Exp. Med.*, 1993, **178**, 749) and in the spontaneous arthritis and nephritis produced in MLR lpr/lpr mice, in which there is also evidence of iNOS induction (Weinberg J.B., *J.Exp. Med.*, 1994, **179**, 651). There are also increases in NOS activity in animal models of inflammatory bowel disease and an inhibitor of NOS ameliorates guinea-pig model ileitis (Boughton-Smith N.K. et al, *Agents and Actions,* 1994, **41**, 223; Miller M.J.S., *J. Pharmacol. Exp. Ther.*, 1993, **264**, 11).

In clinical studies there are increases in the production of NO and in iNOS expression in a variety of chronic inflammatory diseases, such as rheumatoid and osteoarthritis (Farrell A.J. et al, *Ann Rheum. Dis.*, 1992, **51**, 1219; Grabowski P.S. et al, *Arth. & Rheum.*, 1996, **39**, 643; Stichtenoth D.O. et al, *Ann of the Rheumatic Diseases,* 1995, **54**, 820; McInnes I.B. et al, *J. Exp. Med.*, 1996, **184**, 1519), inflammatory bowel disease (Boughton-Smith N.K. et al, *Lancet,* 1993, **342**, 338; Lundberg J.O.N. et al, *Lancet,* 1994, **344**, 1673; Middleton S.J. et al, *Lancet,* 1993, **341**, 465), psoriasis (Rowe A. et al, *Lancet,* 1994, **344**, 1371; Bruch-Gerharz D. et al, *J. Exp. Med.*, 1996, **184**, 2007) and asthma (Hamid, Q. et al, *Lancet*, 1993, **342**, 1510; Barnes J. and Liew F.Y., *Immunol. Today*, 1995, **16**, 128) and iNOS is implicated as a major pathological factor in these chronic inflammatory diseases. Thus, there is considerable evidence that inhibition of excessive NO production by iNOS will be anti-inflammatory. Since the production of NO from eNOS and nNOS is involved in normal

physiology, it is important that any NOS inhibitor used therapeutically for treating inflammation is selective for iNOS. Such an inhibitor will inhibit the excessive production of NO by iNOS without effecting the modulation of blood pressure produced by NO production from eNOS or the non-adrenergic non-cholinergic neuronal transmission produced by NO from nNOS.

The recent discovery of an inducible isoform of cyclooxygenase (COX-2) has provided a specific target for inhibition of inflammatory prostaglandin synthesis while leaving the physiological actions of prostaglandins formed by constitutive cyclooxygenase (COX-1) intact (Fu et al, *J. Biol. Chem.*, 1989, **265**, 16740; DeWitt D., *Biophys. Acta*, 1991, **1083**, 121; Masferrer J.L. and Seibert, *Receptor,* 1994, **94**, 17). Prostaglandins play an important role in inflammation, for example in both the pain and swelling associated with arthritis. The commonly used cyclooxygenase inhibitors or non-steroid anti-inflammatory drugs (NSAIDs) are non-selective in that they reduce prostaglandins involved in inflammatory pain and swelling but also inhibit the physiological prostaglandin formation which is required particularly for maintenance of gastrointestinal integrity. A number of selective COX-2 inhibitors have been described which are anti-inflammatory in a variety of animal models but which, unlike non-selective COX inhibitors, do not produce gastrointestinal pathology.

Since both iNOS and COX-2 inhibitors are selective for the enzyme isoforms induced in inflammation which produce NO and prostaglandins respectively, and will not effect the constitutive enzymes involved in normal physiology, the combination will have a substantially reduced level of adverse side effects associated with NSAIDs and also anti-inflammatory glucocorticoids, which inhibit the induction of both enzymes (Radomski M.V. et *al, Proc. Natl. Acad. Sci. USA,* 1990, **87**, 10043; Masferrer J.L. et al, *J. Clin. Invest.*, 1990, **86**, 1375 ).

Compounds that selectively inhibit COX-2 have been described in US patents 5,380,738; 5,344,991; 5,466,823; 5,434,178; 5,474,995; 5,510,368; 5,521,207 and 5,604,260.